Review article

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SAFETY OF CONCURRENT INTRAVENOUS DRUG APPLICATION

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Simultaneous application of multiple intravenous pharmaceuticals during which they come into direct contact is common in clinical practice. This is done with both intravenous infusions and injections. While it can be practically and clinically justified, this practice can only be safe for patients on the precondition that all of the products being combined are mutually compatible. Physical and chemical incompatibility, with precipitation being the most common and important phenomenon, presents a possible health risk. Intravenous drugs and simple intravenous liquids both have potential for displaying incompatibility. Over time, many studies utilizing various analytical methods have uncovered numerous inadequate combinations. However, the methodology of these studies is very heterogenous; it is not always clear whether the results are clinically relevant and many combinations have not been tested yet. It has also been shown that healthcare providers that are involved in therapy management sometimes do not possess enough knowledge about drug compatibility, though this can be improved with appropriate interventions. Furthermore, a precisely defined protocol for compatibility studies could aid interpretation and comparison of future research data. On the other hand, easily accessible databases and knowledge of alternative application methods for therapy could prevent incompatibilities in everyday work.

Key words

intravenous infusions, intravenous injections drug incompatibility, patient safety

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BEZBEDNOST ISTOVREMENE INTRAVENSKE PRIMENE LEKOVA

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U kliničkoj praksi je uobičajena istovremena primena više lekova za intravenskim putem pri čemu oni stupaju u direktan kontakt. To se čini i sa intravenskim infuzijama i injekcijama. Iako to može biti opravdano iz praktičnih i kliničkih razloga, ova praksa je bezbedna za pacijente samo ako je zadovoljen preduslov da su preparati koji se kombinuju međusobno kompatibilni. Pojava fizičko-hemijskih inkompatibilija, od kojih je najčešća i najznačajnija pojava precipitacije, predstavlja mogući zdravstveni rizik. Intravenski lekovi i intravenske tečnosti jednostavnog sastava jednako poseduju potencijal za ispoljavanje inkompatibilnosti. Vremenom su mnogobrojna ispitivanja utvrdila veći broj nekompatibilnih kombinacija koristeći različite analitičke metode. Ipak, metodologija ovih ispitivanja je veoma heterogena; nejasno je da li su dobijeni rezultati uvek klinički relevantni i pri tom su mnoge kombinacije neispitane. Utvrđeno je da zdravstveni radnici koji su odgovorni za terapiju pacijenata nekada ne poseduju dovoljno znanja o kompatibilnosti lekova, što se može prevazići uz odgovarajuće intervencije. Takođe, precizno definisanje protokola ispitivanja kompatibilnosti može olakšati interpretaciju i upoređivanje podataka dobijenih iz budućih studija. S druge strane, lako dostupne baze podataka i poznavanje alternativnih metoda primene terapije može sprečiti pojavu inkompatibilija u svakodnevnom radu.

Ključne reči

intravenske infuzije, intravenske injekcije inkompatibilnost, bezbednost pacijenata

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Introduction

It is common in everyday clinical practice for patients to recieve multiple drugs at the same time as part of their therapy. Furthermore, parenteral application of drugs is also common in this setting, especially in the form of intravenous injections and infusions (1). Ideally, these dosage forms should be applied separately using a new venous access site each time (2). However, it should be taken into account that intravenous therapy is a specific form of drug application that requires special tools and equipment, as well as trained personnel, time management and a favorable condition of the patient. With that in mind, it is clear why a need for simultaneous application of two or more intravenous drugs – infusions, injections or both – arises in practice (1-3).

The greatest advantage in combining these forms is in critical patients that require many drugs delivered in a short timespan. Depending on the severity of a condition, it is often not possible to secure enough venous access sites in certain patients if each drug must be administered separately (1-2). Even when it is possible, using multiple venous accesses increases the risk of mechanical, infectious and thrombotic complications due to their association with intravenous drug application (4).

Of course, just like any intervention, this practice also carries its risks. The biggest problem lies in the mutual compatibility of the dosage forms being combined. Any unwanted interaction between the drug components being combined represents an incompatibility that manifests itself as a chemical or physical change (1). Naturally, microbiological contamination is also a possibility when dealing with sterile products (4). Looking at incompatibility through these types of changes is typical from the point of view of pharmaceutical technology. Pharmacologically speaking, one can speak of therapeutic incompatibility as well, which manifests itself in the body. However, this is outside of the

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scope of this paper. With that said, the direct contact between two drug formulations can lead to physical and chemical changes that can further impact the efficacy and safety of the overall therapy. This is why having reliable information about the compatibility of two drugs is required to assure their safe application (1).

Combining intravenous forms

It should be defined what exactly is meant by combining or mixing two or more intravenous drugs. Two methods that are used in practice fit this description. The first method is used in patients receiving an infusion to which new infusions or injections need to be added. Depending on the dosage form, they are connected or are directly injected in the infusion set carrying the primary infusion via injection and Y-site ports (1, 3). The connectors that are used are usually Y-shaped, which means that two formulations being applied meet at the intersection and are mixed before entering the bloodstream. Time of contact between then is relatively short (ranging from 1-2 minutes to an hour), which is why physical incompatibility is the more important negative outcome when utilizing this method compared to chemical incompatibility, which often requires more time to result in significant change. This compatibility is referred to as Y-site compatibility (1, 2).

The second method is more direct and involves adding a sterile drug to an infusion before application. Injections can be mixed in a similar way. These preparations are often done in a hospital pharmacy. Since in this instance time of contact is usually longer (measured in hours or days), more attention is given to chemical compatibility (1, 2, 5).

Regardless of which method is employed, the intravenous forms being combined are not just drug solutions, but also simple intravenous fluids. This is why incompatibility is not limited just to interactions between two or more active ingredients. In fact, intravenous fluids are often the primary infusion with the role (among others) of being the carrier of any additional

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therapy. Additionally, these solutions are used for diluting, reconstituting and directly mixing drugs. However, despite their simple composition (consisting of electrolytes, glucose and related compounds), intravenous fluids have the potential to interact with drug molecules and therefore cannot be considered inert (1, 3). In a larger sense, packaging material and excipients can also be a source of incompatibility. While most intravenous dosage forms are solutions, some emulsions can also be delivered in this manner. Compatibility considerations become even more complicated for complex pharmaceuticals such as parenteral nutrition – emulsion or not. The same can be said for blood products (3).

Forms of incompatibility

Physical incompatibility most often presents as precipitation, turbidity, color change, gas formation or change in pH level. It can be visible and is often accompanied by chemical changes. Precipitation is the most important incompatibility-related phenomenon and oftentimes occurs as a result of pH change. Many parenteral forms are buffered, but their buffer capacity is limited. By mixing two solutions of significantly different pH levels, a change in drug ionization (in the case of weak acids and bases) occurs, leading to changes in solubility and consequently precipitate formation (3, 5).

Precipitates can also be formed in ion exchange reactions, e.g. when polyvalent cations from one solution displace monovalent cations from another. They can also form when the end result post-mixing is a solvent in which one of the drugs is poorly soluble (3, 5). Precipitate formation is the most common manifestation of incompatibility and presents a serious problem as it can lead to embolism if the particles formed enter the systemic circulation. Smaller particles can also cause organ damage due to the occlusion of small blood vessels. Overall, this leads to an increase in patient morbidity in cases where precipitation occurs during therapy. Local reactions such as phlebitis are less severe (6, 7). On the other hand,

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precipitates can also be a purely technical problem in instances where they cause mechanical blockage in an infusion set which stops further drug delivery (7).

Changes in pH can happen without concomitant precipitation, but they are still an unwanted event. Gas formation can be dangerous as a potential cause of gas embolism. This frequently crops up in the form of carbon dioxide release in scenarios when one of the formulations being combined contains bicarbonates (2, 3, 8). In cases of incompatibility, emulsions display instabilities specific to their pharmaceutical form (creaming, sedimentation, phase separation and others) (2, 3).

Chemical incompatibility is frequently not visible and is a result of chemical degradation reactions typical for drug molecules – oxidation, reduction and hydrolysis. Packaging incompatibility can also be put in this category. Most of the time, drug degradation is considered significant when there is a loss of active ingredient larger than 10% or a toxic product has formed. As a consequence, this leads to a reduction in the therapeutic effect or possible toxicity (3, 6, 9). Changes in pH level and external factors, such as temperature, light and oxygen, can have a crucial effect on the rate of chemical change. Biologic drugs are especially sensitive to changes in internal and external conditions and, as a rule, are generally not mixed with other drugs (3).

In practice

Many studies looked at various individual drug combinations and their compatibility (2, 6, 10-12). Likewise, research has been done on the occurrence of incompatibility in clinical practice, with the results being highly variable. One study showed that 7,2% of all intravenous drug combinations used were incompatible in one clinical setting, while another gave a finding of 15% (13, 14). It should be clear that the drugs being looked at in these studies are those that are most often used in everyday clinical work – particularly in intensive

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care units which require complex treatment plans. Table 1 lists certain examples of incompatibility along with the mechanisms of their formation.

Table 1. Examples of incompatibility encountered in practice

Drug-drug combination	Consequence of incompatibility
heparin and many antibiotics (15)	precipitate formation
beta-lactams and vancomycin (16)	
furosemide and low-pH solutions (3)	
Ringer's solution and many drugs (17)	
metoclopramide and sodium bicarbonate (3)	gas formation
pantoprazole and many drugs (12)	color change and precipitate formation
adrenaline and sodium bicarbonate (18)	inactivation of adrenaline
atracurium and high-pH solutions (3)	inactivation of atracurium
midazolam and hydrocortisone (11)	loss of hydrocortisone
diazepam and PVC (19)	sorption to packaging
propofol and lidocaine (20)	droplet coalescence and phase separation of emulsion

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It is also noticeable from systematic reviews in this area that certain drugs have a particular tendency to interact, such as vancomycin, hydrocortisone, pantoprazole and in general drugs whose solutions are highly acidic or basic (10-12). However, there is not always a strict distinction between "allowed" and "unallowed" combinations, as compatibility issues can sometimes be overcome with certain modifications in the drug mixing process. Time of contact, concentration of reacting components and type of solvent are all factors that

determine whether a borderline incompatibility will manifest itself or not (2-3, 10). On the other hand, there are also situations when different studies give conflicting results about the compatibility of a certain drug combination (2, 12).

Parenteral nutrition products are a challenge of their own. There are several types of them that can be commercially acquired, but they can also be prepared in hospital pharmacies. It is useful to make a distinction between formulations without lipid components (solutions) and those that contain them (emulsions). Regardless whether they are all-in-one or are applied separately, they have a high potential for drug compatibility issues due to their complex composition. For example, trace elements can act as catalysts in degradation reactions, while any change in the calcium ion – phosphate ratio can result in precipitate formation. Of course, other components can be a source of instability as well. Special attention should be given to lipid formulations, as drugs that are stable in non-lipid forms can become unstable in the presence of lipids. Generally, mixing drugs and parenteral nutrition products should be avoided. Nevertheless, this practice is common in pediatric medicine when securing multiple venous access sites is not possible (21-22).

There is even less data in literature about adding intravenous drugs to blood products. In fact, this practice is banned in many hospitals (23). For this reason they are generally not mixed together and the same applies to biologic therapy (3, 23).

Uncovering incompatibility

Although the term incompatibility is related to the term stability, stability guidelines laid out by the International Council for Harmonisation (ICH) do not require manufacturers to assess the compatibility of their drugs with other products, including intravenous drugs (24). However, since many intravenous drugs require in-use stability testing, this process can be

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used to determine whether a drug is compatible with various intravenous solutions that are used as a solvent or diluent (25).

Data on intravenous compatibility has been gathered from experience, but also formal studies of various drug combinations. These studies are based on monitoring physical and chemical stability. As there is no standardized protocol for them, researchers choose which parameters and analytical methods to employ during the study. Physical stability is usually determined by monitoring for precipitation formation, color change, gas bubbles and changes in pH level. Precipitates can be detected visually, but it is better to use nephelometry or turbidimetry. Color change is a visually qualitative change that can be quantified with certain instrumental methods, such as spectrophotometry. Changes in pH levels can be measured with a pH-meter. Chemical changes are often detected with the help of HPLC. However, studies look at physical changes most of the time, as in practice it is more common to mix drugs through a concurrent infusion rather than directly, where chemical stability would be more important (2, 10, 11, 26).

The main downside of these studies is the heterogeneity of their methodologies. Each study makes its own choice on which parameters to follow and which analytical methods to utilize. Furthermore, it is not always clear whether the results are clinically relevant due the way the study was conducted. One paper showed that researchers often monitor for physical changes after hours of mutual contact, even though in practice the time of contact is much less than that. The same paper showed that none of the studies reviewed had a blinded design without which potential bias cannot be overlooked (2). The American Journal of Health-System Pharmacy recently published guidelines on stability and compatibility testing that touch on the area of intravenous incompatibility. The article deals with, among other things, sample preparation, variation of external factors and testing the impact of packaging on

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compatibility (26). Guidelines such as these could prove to be very useful for standardizing future research in the area of incompatibility.

Preventing incompatibility

Actively preventing drug incompatibility is an imperative of safe clinical practice. A necessary precondition for this to be achieved is knowing ahead of time whether a certain combination of products is compatible. If an interaction is possible, and the combination of drugs is necessary and justified, an intervention can be made on several levels (27). When possible, an alternative, non-interacting dosage form should be used. Similarly, a drug can be switched with one that is compatible (3).

If the intravenous route is in fact needed, an attempt should be made to separate the two formulations by time or space. That can mean using a different venous access site to apply the second drug (2). However, nowadays there is the option of using multi-lumen catheters that contain several spatially separated lumens in one tube, which enables the separate and simultaneous delivery of multiple intravenous drugs (3, 13). Another option are in-line filters built into infusion sets that prevent particles above a certain size (like those from precipitates) from passing over to the bloodstream (28).

Conversely, incompatible drugs can sometimes also be separated by time of application. In those instances, the infusion set does not have to be changed if it is flushed with an appropriate sterile solution, before and after the incompatible drug is applied (29).

Healthcare workers that are involved in drug application are responsible for checking the compatibility of two or more products before combining them. However, hospital pharmacists also play an important role as they should be able to provide information on compatibility (12, 27). Several studies have shown that in practice knowledge about compatibility is not always satisfactory in practice, although there is less data on the actual

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clinical consequences of wrong practice (6, 11, 13, 14). Nevertheless, it has been shown that the frequency of compatibility issues can be significantly reduced after applying educational and preventative measures (11, 13, 14).

Official recommendations exist both on higher and lower levels. For example, the Royal College of Nursing in the United Kingdom has published guidelines that touch on intravenous therapy compatibility (29). On the other hand, hospitals can have their in-house guidelines and protocols that deal with this matter. These recommendations are often presented in the form of tables and graphs that are easily accessible to healthcare providers (30). Still, there are faster and simpler ways to obtain the necessary facts. For example, Micromedex and Lexicomp are online services that offer a compatibility database upon registration. Stabilis is an online database that anyone can access (9, 31, 32). The data in these databases are supported by references to the original papers where the combinations were tested. Of course, the quality of the data is directly correlated with the conception and methodology of the source studies. As mentioned before, there are certain issues with studies in this field. Another big problem is the fact that the number of possible drug combinations is huge, even when only considering two-part combinations of a limited amount of drugs. With that in mind, many combinations have not been tested yet and therefore are generally not tried out in practice before enough information about them is generated (2, 10, 11).

Conclusion

Combining intravenous drugs can be safe in cases when this practice is justified only when the precondition of mutual compatibility is met. A large number of guidelines and easily accessible databases allow for a fast check on the adequacy of a certain combination during everyday work. Simultaneously, raising awareness on the possibility of incompatibility, its types and ways to recognize and prevent it can decrease its frequency along with the

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associated health risks. However, as guidelines in this area are based on the results on individual research, there is a need to define a standard protocol for compatibility testing so that the data generated can be better evaluated and compared.

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References

1. Murney P. To mix or not to mix - Compatibilities of parenteral drug solutions. Aust Prescr 2008;31:98-101. Available at: https://doi.org/10.18773/austprescr.2008.057.

2. Kanji S, Lam J, Johanson C, Singh A, Goddard R, Fairbairn J, et al. Systematic review of physical and chemical compatibility of commonly used medications administered by continuous infusion in intensive care units. Crit Care Med 2010;38(9):1890–8. Available at: https://doi.org/10.1097/CCM.0b013e3181e8adcc.

3. Bentley J, Heard K, Collins G, Chung C. Mixing medicines: how to ensure patient safety. Pharm J 2015;294. Available at: https://doi.org/10.1211/pj.2015.20068289.

4. McGee D, Gould M. Preventing complications of central venous catheterization. N Engl J Med 2003;348(12):1123–33. Available at: https://doi.org/10.1056/NEJMra011883.

5. Newton D. Drug incompatibility chemistry. Am J Health Syst Pharm 2009;66:348–57. Available at: https://doi.org/10.2146/ajhp080059.

6. Benlabed M, Perez M, Gaudy R, Genay S, Lannoy D, Barthélémy C, et al. Clinical implications of intravenous drug incompatibilities in critically ill patients. Anaesth Crit Care Pain Med 2019;38(2):173–80. Available at: https://doi.org/10.1016/j.accpm.2018.04.003.

7. Hanifah S, Ball P, Kennedy R. Management of Y-Site Incompatibility of Intravenous Medication: A Scoping Review. Indonesian J Pharm 2022;33(3):353-65. Available at: https://doi.org/10.22146/ijp.2262.

8. Pant D, Narani KK, Sood J. Significant air embolism: A possibility even with collapsible intravenous fluid containers when used with rapid infuser system. Indian J Anaesth 2010;54(1):49–51. Available at: https://doi.org/10.4103/0019-5049.60498.

9. Wolters Kluwer. I.V. Compatibility [Internet]. Wolters Kluwer 2023; [cited 2023 Oct 07]. Available from: https://www.wolterskluwer.com/en/solutions/lexicomp/resources/facts-comparisons-user-academy/trissels-iv-compatibility-databases.

10. Lao GC, Reyes MR, Turet JR, Dot MP, Muner DS, Cabezas CL. Compatibility of drugs administered as Y-site infusion in intensive care units: A systematic review. Med Intensiva (Engl Ed) 2020;44(2):80-7. Available at: https://doi.org/10.1016/j.medin.2018.08.004.

11. Marsilio NR, Silva D, Bueno D. Drug incompatibilities in the adult intensive care unit of a university hospital. Rev Bras Ter Intensiva 2016;28(2):147–53. Available at: https://doi.org/10.5935/0103-507X.20160029.

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12. Maison O, Tardy C, Cabelguenne D, Parat S, Ducastelle S, Piriou V, et al. Drug incompatibilities in intravenous therapy: evaluation and proposition of preventive tools in intensive care and hematology units. Eur J Clin Pharmacol 2019;75(2):179–87. Available at: https://doi.org/10.1007/s00228-018-2602-6.

13. Bertsche T, Mayer Y, Stahl R, Hoppe-Tichy T, Encke J, Haefeli WE. Prevention of intravenous drug incompatibilities in an intensive care unit. American Journal of Health-System Pharmacy 2008;65(19):1834–40. Available at: https://doi.org/10.2146/ajhp070633.

14. Vogel Kahmann I, Bürki R, Denzler U, Höfler A, Schmid A, Splisgardt H. Incompatibility reactions in the intensive care unit. Five years after the implementation of a simple "colour code system". Anaesthesist 2003;52(5):409–12. Available at: https://doi.org/10.1007/s00101-003-0481-3.

15. Droste JC, Jeraj HA, MacDonald A, Farrington K. Stability and in vitro efficacy of antibiotic-heparin lock solutions potentially useful for treatment of central venous catheter-related sepsis. J Antimicrob Chemother 2003;51(4):849–55. Available at: https://doi.org/10.1093/jac/dkg179.

16. Raverdy V, Ampe E, Hecq JD, Tulkens PM. Stability and compatibility of vancomycin for administration by continuous infusion. J Antimicrob Chemother 2013;68(5):1179–82. Available at: https://doi.org/10.1093/jac/dks510.

17. Vallée M, Barthélémy I, Friciu M, Pelletier É, Forest JM, Benoit F, et al. Compatibility of Lactated Ringer's Injection With 94 Selected Intravenous Drugs During Simulated Y-site Administration. Hosp Pharm 2021;56(4):228–34. Available at: https://doi.org/10.1177/0018578719888913.

18. Bonhomme L, Benhamou D, Comoy E, Preaux N. Stability of epinephrine in alkalinized solutions. Ann of Emerg Med 1990;19(11):1242–44. Available at: https://doi.org/10.1016/s0196-0644(05)82281-4.

19. Jin SE, You S, Jeon S, Hwang SJ. Diazepam sorption to PVC- and non-PVC-based tubes in administration sets with quantitative determination using a high-performance liquid chromatographic method. Int J Pharm 2016;506(1-2):414–19. Available at: https://doi.org/10.1016/j.ijpharm.2016.04.040.

20. Masaki Y, Tanaka M, Nishikawa T. Physicochemical compatibility of propofol-lidocaine mixture. Anesth Analg 2003;97(6):1646–51. Available at: https://10.1213/01.ANE.0000087802.50796.FB.

21. Sacks G. Drug-Nutrient Considerations in Patients Receiving Parenteral and Enteral Nutrition. Pract Gastroenterol 2004;28(7):39-48.

22. Farhan M, McCallion N, Bennett J, Cram A, O'Brien F. Stability and compatibility of parenteral nutrition solutions; a review of influencing factors. Eur J Pharm Biopharm 2023;187:87–95. Available at: https://doi.org/10.1016/j.ejpb.2023.04.002.

AMM Paper Accepted

23. Birch C, Hogan C, Mahoney G. Co-administration of drugs and blood products. Anaesth Intensive Care 2001;29(2):137-40. Available at: https://doi.org/10.1177/0310057X0102900207.

24. ICH. Q1A (R1) Stability testing of new drug substances and drug products. ICH 2003.

25. Committee for Medicinal Products for Human Use. Note for guidance on in-use stability testing on human medicinal products. EMEA 2001.

26. McPherson T, Kolling W. Stability and compatibility study guidelines for AJHP. *Am J Health Sys Pharm 2023*;80(18):1271–74. Available at: https://doi.org/10.1093/ajhp/zxad132.

27. Department of Health (UK). *Mixing of medicines prior to administration in clinical practice: medical and non-medical prescribing.* Department of Health 2010.

28. Jack T, Boehne M, Brent BE, Hoy L, Köditz H, Wessel A, et al. In-line filtration reduces severe complications and length of stay on pediatric intensive care unit: a prospective, randomized, controlled trial. Intensive Care Med 2012;38(6):1008-16. Available at: https://doi.org/10.1007/s00134-012-2539-7.

29. Royal College of Nursing. Standards for Infusion Therapy. Royal College of Nursing 2016.

30. Kondo M, Tanaka C, Tagami T, Nagano M, Sugaya K, Tagui N, et al. Utility of a Compatibility Chart for Continuous Infusions in the Intensive Care Unit. J Nippon Med Sch 2022;89(2):227-32. Available at: https://doi.org/10.1272/jnms.JNMS.2022_89-220.

31. Merative. Micromedex [Internet]. Merative 2023; [cited 07.10.2023]. Available from: https://www.micromedexsolutions.com/home/dispatch.

32. Vigneron J, Gindre I, Daouphars M, Demoré B, Monfort P, Barbier P, et al. Stabilis [Internet]. Stabilis 2023; [cited 07.10.2023]. Available from: https://www.stabilis.org/.

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